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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/700,971	11/04/2003	Muthiah Manoharan	CHEM0005US.P1	4943

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EXAMINER	
MCGARRY, SEAN	
ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
03/02/2012	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

eofficemonitor@woodcock.com

Office Action Summary	Application No.	Applicant(s)	
	10/700,971	MANOHARAN ET AL.	
	Examiner	Art Unit	
	SEAN MCGARRY	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 February 2012*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,4,9,101 and 110-114* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1, 4, 9, 101, and 110-114* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Official Action considers the response filed 2/16/2012. Applicant arguments filed 2/16/2012 have been considered and are not found convincing. The arguments are addressed below.

Priority

The priority granted for the instant claims remains 7/09/03 which is based on priority application 10/616,241.

Applicant has again amended the claims and refers to the 08/870,608 application to point to support for the instant invention. The examiner does not agree that the cited portions of the 08\870,608 application provide support for the instantly claimed invention.

Applicants arguments in regard to the specific modifications now recited in the claims in the context of a double stranded RNA substrate are accepted. However, the arguments and citations are insufficient to establish possession of double stranded oligonucleotides with a “conjugate group” with or without the recited modifications and

furthermore there is simply no support for double stranded RNA compounds as pharmaceuticals in the 08/870,608 application.

It is also noted that the basis for support for the double stranded RNA compounds recited does indeed lie within example 27-a, 27b and 28 which disclosure refers to a double stranded RNA substrate made for the purpose of testing an double stranded RNAse where the compounds are of a specific size range and employ modifications to serve specific purpose where the modifications taught otherwise in the specification are not utilized or could not be utilized as per the purpose of the compounds of Example 27a, for example.

The specification, after the Example 27a refers to the double stranded RNAs to be used in affinity columns, for example. See also originally presented claims 81 and 82 of the '608 application. The utility provided for the double stranded compounds in the '608 application is for detecting and isolating an double stranded RNAse.

There is not teaching or disclosure for the addition of a "conjugate group" to a double stranded RNA substrate that would be consistent with the support provided in the portions of the '608 application relied upon by applicant. It is noted that there is no literal support and further there is no readily apparent support when the specification and claims of the '608 application is considered as a whole. It is noted that the only portion of the '608 specification cited by applicant [in their previous response] in support of the "conjugate group" is page 26. It is noted that this portion of the specification teaches that equipment for oligonucleotide synthesis was known at the time of invention of the '608 application. A look at the paragraph preceding it is clear that the equipment

is noted for making “The oligoribonucleotides and oligoribonucleosides used in accordance with this invention. . .". Applicant provides no argument in the instant response to provide any support for the “conjugate group” recited in the claims.

Applicant has not provided any support or evidence for a double stranded RNA as a pharmaceutical. Applicant asserts that any description of modifications in the ‘608 application must be considered for both single stranded and doublestranded compounds. This position is not agreed with. The ‘608 application , when considered as a whole , provided a description of single stranded RNA or RNA-like oligomers for use to hybridize to a target RNA for cleavage by a double stranded RNAse protein. Nowhere in the application is there a description of a double stranded oligonucleotide for use as a pharmaceutical. For example, when one reads the summary of The Invention section of the ‘608 application it is stated “In accordance with this invention there are provided oligomeric compounds formed from a linear sequence of linked ribonucleotides that are specifically hybridizable to a preselected RNA target.” At page 16 it is stated “It has now been found that the oligomeric compounds of the invention have certain RNA like features that allow them to form double stranded structure with a targeted RNA region and the double stranded structure is subsequently degraded . . .” At page 20 it is stated “Thus the compounds of the invention can be used to modulate the expression of any suitable target RNA. . .” The description provided in the specification clearly is drawn to single stranded compounds for use as inhibitory compounds.

It is noted that only in claims 78-80 and in examples 27-29 are double stranded oligonucleotides taught. The rest of the specification and claims are drawn to single

stranded RNA oligomers for use in hybridizing to a target RNA to inhibit expression. Nowhere else in the specification is a double stranded oligomer described. In the Example 27-29 the double stranded oligomers are described a substrate RNA. The only utility taught for these double stranded oligomers is for use in affinity columns and for use in dsRNAse detection. The specification, taken as a whole , clearly differentiats between the invention drawn to an oligomer for use in inhibiting target RNA and a description of a double stranded RNA substrate with a specific structure for use in affinity columns or for use in dsRNAse detection where there is no teaching for conjugate groups or for pharmaceutical applications for double stranded RNAs.

Applicant argues that the priority reference must be considered in its entirety, ie it must be considered as a whole. It is with this type of consideration in view of the portions cited by applicant that priority for the claimed invention is denied to the 08/870,608 application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 9, 101, and 110-114 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Tuschl et al [US 2004/0259247], Woolf et al [US20040054155], Schwarz et al[Molecular Cell, Vol.10:537-548,9/2002] et al and Manoharan et al[Manoharan, M. Antisense Drug Technology, Principles, Strategies, and Applications, Crooke, S. T. ed., Marcel Dekker, New York 2001, Chapter16, pages 391-467, cited by applicant].

The claimed invention is as clearly set forth in the claims.

Tuschl et al have taught the use of siRNA molecules for the inhibition of a desired target nucleic acid. It has been taught that the preferred length of these double stranded RNAs is 19-25 nucleotides. It has been taught at paragraph 15 and 179-181 what positions of an siRNA molecule are important for function and what areas are modifiable such as 5' and/or 3' ends. Tuschl also teach that known modifications such

as 2'-O modifications can be used in siRNA compounds. For example, 2'-O modifications can be used at the 3'and/or 5' end of the oligonucleotides in an siRNA. It has been taught to use siRNA in cell culture to determine gene function, for example (see paragraphs 28 and 29, for example). At paragraph 16 it has also, for example, ben taught that phosphorothioate linkages can be used in siRNA compounds. Tuschl et al have taught at paragraphs 28-33 that carrier mediated delivery is an option for siRNA introduction into cells(see paragraph 33, for example). Tuschl et al do not specifically teach conjugates.

Manoharan has taught the use of Lipidic nucleic acids where it has been taught the use of moieties such as cholesterol linked to terminal ends, backbones or bases of antisense oligonucleotides where it is asserted these provide for more efficient antisense administration to cells. It has been taught that attachment at the 2' position of an oligonucleotide should minimize interference with hybridization. Manoharan et al has shown that it was well established at the time of invention to utilize cholesterol as a means to mediate cellular delivery of oligonucleotides. It has been taught by Monoharen et al that cholesterol can be attached to the 3' end or 5' end of an oligonucleotide.

Woolf et al have taught siRNA compounds and further teach that cholesterol moieties as well as many other moieties can be attached to siRNA compounds for enhanced uptake into cells in vitro and in vivo. Woolf et al teach for example:

Detail Description Paragraph:

[0144] Conjugating agents bind to the oligonucleotide in a covalent manner. In one embodiment, oligonucleotides can be derivitized or chemically modified by binding to a

conjugating agent to facilitate cellular uptake. For example, covalent linkage of a cholesterol moiety to an oligonucleotide can improve cellular uptake by 5- to 10-fold which in turn improves DNA binding by about 10-fold (Boutorin et al., 1989, FEBS Letters 254:129-132). Conjugation of octyl, dodecyl, and octadecyl residues enhances cellular uptake by 3-, 4-, and 10-fold as compared to unmodified oligonucleotides (Vlassov et al., 1994, Biochimica et Biophysica Acta 1197:95-108). Similarly, derivatization of oligonucleotides with poly-L-lysine can aid oligonucleotide uptake by cells (Schell, 1974, Biochem. Biophys. Acta 340:323, and Lemaitre et al., 1987, Proc. Natl. Acad. Sci. USA 84:648).

Detail Description Paragraph:

[0145] Certain protein carriers can also facilitate cellular uptake of oligonucleotides, including, for example, serum albumin, nuclear proteins possessing signals for transport to the nucleus, and viral or bacterial proteins capable of cell membrane penetration. Therefore, protein carriers are useful when associated with or linked to the oligonucleotides. Accordingly, the present invention provides for derivatization of oligonucleotides with groups capable of facilitating cellular uptake, including hydrocarbons and non-polar groups, cholesterol, long chain alcohols (i.e., hexanol), poly-L-lysine and proteins, as well as other aryl or steroid groups and polycations having analogous beneficial effects, such as phenyl or naphthyl groups, quinoline, anthracene or phenanthracene groups, fatty acids, fatty alcohols and sesquiterpenes, diterpenes and steroids. A major advantage of using conjugating agents is to increase

the initial membrane interaction that leads to a greater cellular accumulation of oligonucleotides.

Schwarz et al have taught that the 3' end of an antisense strand of a siRNA compound can be blocked and still provide adequate inhibition of its target. Schwarz also teach the importance of not blocking the 5' end of the antisense strand of a siRNA.

One in the art would clearly combine the teachings of Tuschl, Woolf et al, and Manoharan et al to make the instant invention since Tuschl has taught the use of siRNA in cells. Manoharan provide a teaching of how to make and use lipidic moieties in oligonucleotides for enhanced cellular delivery and Tuschl et al have taught locations where siRNAs can be modified, where Schwarz et al have shown that the 3' end of the antisense strand can be modified while the 5' end of the antisense strand is preferably not. Woolf et al have taught that one in the art can apply cholesterol moieties to an siRNA compound to facilitate delivery to cells. The prior art teaches that the use of such conjugates was known in the art to enhance delivery of nucleic acid into cells, for example. The determination of which strand or both strands to add substituents would clearly have been a matter of optimization as the general use of substituents as claimed was established in the art at the time of invention. Tuschl and Schwarz et al have provided a clear basis for the locations of modification in a siRNA. The claimed invention appears to amount to the use of a known oligonucleotide delivery method [cholesterol conjugation] and a known oligonucleotide that would be delivered to cells[siRNA]. It is noted that applicant has no working examples of the invention as claimed, and the prior art provides substantially the same level of teaching as the

instant specification, where both the prior art [Woolf et a]l and the instant specification teach that any of a multitude of moieties can be attached to siRNA compounds for enhanced delivery and targeting.

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Applicant's arguments filed 2/16/2012 have been fully considered but they are not persuasive. Applicant arguments are based on the arguments of priority addressed above.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SEAN MCGARRY whose telephone number is (571)272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Heather Calamita can be reached on (571) 272-2876. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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